~~TACGGACGGAAACTGTTTTTTTTTTTT~~; (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

Sub. D13

--65. (New) The method of claim 57, wherein the primer in step (B)(1) has the sequence AGGATCAACAACAACCAGTA.--

--66. (New) The method of claim 57, wherein the primer in step (B)(2) has the sequence ATCGTCCTGGGCTTTCGCAA.--

--67. (New) The method of claim 57, wherein the fluorescent dye which is linked to the primer in step (B)(2) is Texas red.--

C4 concld

--68. (New) The method of claim 57, wherein the sample is a serum sample.--

REMARKS

Claims 1-18 are pending in the subject application. Applicants have herein canceled claims 1-18 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application and added new claims 19-68. Such amendment is made to more clearly point out the subject matter of the claimed invention and not in response to the rejections raised in the Office Action. Applicants contend that this amendment does not involve any issue of new matter. Support for these claims may be found inter alia in the specification as follows: claims 19-23: page 9, lines 14-35; claims 24-25: page 14, lines 26-29; claim 26:

page 9, lines 14-35, page 14, lines 26-29; claims 27-32: page 9, lines 14-35; claims 33-34: page 14, lines 26-29; claim 35: page 9, lines 14-35, page 14, lines 26-29; claims 36-43: page 10, lines 10-24, page 16, line 20 to page 17, line 3; claims 44-68: page 14, line 31 to page 18, line 21, page 9, lines 14-35, page 14, lines 26-29; page 11, line 15. In addition, applicants have herein amended the specification to remove references to the word "claim" in accordance with the Examiner's suggestions. Applicants respectfully request entry of this amendment such that claims 19-68 will be pending.

Objections to the Disclosure

The Examiner stated that the disclosure is objected to because of the following informalities: The Examiner stated that the disclosure at least at page 9, line 19; at page 12, line 28; and at page 14, line 32 improperly makes reference to a claim by number. The Examiner stated that there may be other such references as well. The Examiner stated that applicant is requested to review the specification and to delete any reference to claim numbers and, if necessary, to amend the specification to include any material that is only presented as part of a claim. The Examiner stated that Appropriate correction is required.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the specification in accordance with the Examiner's rejections. Applicants contend that these amendments obviate the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Objections to the claims

The Examiner objected to claims 2, 15, and 18 because of the following alleged informalities. The Examiner that claim 2, last line, recites "the said ..." which expression is redundant. The Examiner stated that claim 15, line 6, also recites *the said . . ." . The Examiner stated that in claims 2 and 15, either "the" or "said" should be deleted. The Examiner stated that claim 18 is of improper from because it has improper punctuation because a claim should have a period only at the end. The Examiner stated that claim 18 is also improper because it recites a complete sentence within the claim (lines 4-9).

The Examiner stated that appropriate correction is required.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein canceled claims 1-18 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application and added new claims 19-68. Applicants contend that these amendments obviate the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Rejection under 35 U.S.C. 112, second paragraph

The Examiner stated rejected claims 1-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claim 1 is

indefinite because it is not clear how many synthetic oligonucleotides represent a "set" as recited. The Examiner stated that further, the claim is confusing because it recites a 5' and 3' oligonucleotide; it is not clear whether the cited expression represents one oligonucleotide or two oligonucleotides. The Examiner stated that claim 1 is further indefinite because it recites "the 3' oligonucleotide with an appropriate size"; it is not clear for what purpose the size of the oligonucleotide would be appropriate, nor is it apparent what size(s) would be inappropriate. The Examiner stated that the metes and bounds are indefinite. The Examiner stated that claim 2 is indefinite in reciting "the 5' sequence has the sequence . . ."; The Examiner stated that it is not clear whether "has" should be interpreted as open language, equivalent to "comprises" or closed language, equivalent to "consists of." The Examiner stated that claim 3 is similarly indefinite in reciting "the 3' sequence has sequence...": it is not clear whether has should be interpreted as open language, equivalent to "comprises" or closed language, equivalent to "consists of." The Examiner stated that claim 5 is indefinite because it recites "A method of determining the presence of ... in a sample comprising ..." but does not recite sufficient active process steps to result in a method of determining, nor does it recite any correlation between results obtained in any detecting step, for example, and the preamble or purpose of the claimed method. The Examiner stated that claim 7 is indefinite in reciting "appropriate size"; The Examiner stated that it is not clear for what purpose the size is intended to be appropriate. The Examiner stated that claim 7 is indefinite and apparently has an omitted word because line 8 recites "... is with a fluorescent dye ...".

The Examiner stated that claim 9 is indefinite in reciting "A set of oligonucleotides . . .."; it is not clear how many oligonucleotides are in a set. The Examiner stated that claim 12 is indefinite because it recites "A method to screen for . . ." but does not recite any active process steps. The Examiner stated that Claim 13 is indefinite because it recites "A method to screen for ..." but does not recite any active process steps. The Examiner stated that claim 15 is indefinite in reciting "A set of oligonucleotides ..."; it is not clear how many oligonucleotides make up a set. The Examiner stated that claim 15 is indefinite in reciting in lines 3 and 4, "the size ... should be ..."; The Examiner stated that it is unclear whether a size limitation is being claimed or suggested.

The Examiner stated that claim 15 is indefinite in reciting in line 6, "product should cover ..." and in lines 6-7, "in particular." The Examiner stated that it is unclear whether the material following "should cover" and "in particular" are being claimed or suggested. The Examiner stated that claim 16 is indefinite in reciting "A method to amplify ..." but does not recite any active process steps that would result in amplification. The Examiner stated that claim 17 is indefinite in reciting "A set of oligonucleotides ..."; The Examiner stated that it is not clear how many oligonucleotides make up a set. The Examiner stated that Claim 17 is indefinite in reciting in lines 3 and 4, "the size...should be..."; The Examiner stated that it is unclear whether a size limitation is being claimed or suggested. The Examiner stated that claim 17 is indefinite in reciting in line 6, ""product should cover ...". The Examiner stated that Claim 18 is

indefinite in reciting "A method to amplify ..." but does not recite any active process steps that would result in amplification.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein canceled claims 1-18 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application and added new claims 19-68. Applicants submit that newly added claims 19-68 are not indefinite and do particularly point out and distinctly claim the subject matter of the claimed invention. Applicants contend that these amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 1-18 under 35 U.S.C. 103(a) as being unpatentable over WO 97/40193 to Stuyver et al.,cited on PTO 892, attached. The Examiner stated that Stuyver et al. teach a method for detection of mutant HBV sequence in a sample comprising using primers, if necessary, to amplify the region(s) that bear mutations of interest and using appropriate specific probes, preferably about 10-25 nucleotides long, corresponding to the region bearing the mutation and its wild-type counterpart for hybridizing to the nucleic acids that are in the sample or are amplified from the sample. The Examiner stated that Fig. 1
presents nucleotide sequences for a number of HBV strains; sheet 4 of Fig. 1 discloses the nucleotide sequences that encode HBsAg

and indicates the location of codon 145. The Examiner stated that Stuyver discloses solid supports, including beads or chips, for immobilizing oligonucleotide probes, and also discloses that the oligonucleotides may be modified in order to facilitate immobilization or in order to improve hybridization. The Examiner stated that such modifications include homopolymer tailing, coupling with reactive groups, or coupling such substances as biotin. Oligonucleotides to be used as primers or probes may also be labeled. The Examiner stated that see, e.g., page 16, lines 5-20.'*Table 1, page 28, indicates examples of HBsAg primers (SEQ ID NO's 75, 76, 94, 104, 105) and probes for HBsAg codon 145 wild type and mutant sequences (SEQ ID NO's 77-82). The Examiner stated that based on the teachings of Stuyver et al., it would have been obvious to one of ordinary skill in the art to have made and used primers for amplifying the codon 145 region for one or more HBV strains of interest and to have made, immobilized, and used probes for detecting the presence or absence of escape mutants in HBsAg codon 145 because Stuyver et al. suggests doing so. The Examiner stated that while the primers and probes disclosed by Stuyver are not identical to those instantly claimed, it would have been obvious to one of ordinary skill in the art to have selected other, similar, HBsAg primers and probes that include the flanking regions of codon 145 and the sequences that encode the wild type and the escape mutant codon 145 based on the extensive teachings of Stuyver and to have successfully detected the mutation of interest. The Examiner stated that U.S. Patent 5,955,598 to Birkenmeyer et al., cited on PTO 892, attached, discloses primers and a method for detecting a mutation in HBsAg codon 145 by amplifying and quantitatively detecting the nucleic acid sequences of interest.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein canceled claims 1-18 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application and added new claims 19-68. Applicants maintain that newly added claims are neither anticipated nor rendered obvious by the cited reference, namely Stuyver et al.

Applicants point out that the claimed invention relates to immobilized oligonucleotides which can detect labeled PCR amplified nucleic acids which encode either a mutant or a wildtype human hepatitis B virus surface antigens, and methods of screening samples too identify those having either wildtype or mutant human ~~herpesvirus~~ hepatitis B virus surface antigens. In contrast, the cited reference does not disclose or suggest such. The cited reference at most may describe PCR amplification of samples which may then be screened using labeled probes (see examples 1 and 2 on pages 33-34) . However, the claims of the subject application differ in that (1) the claimed invention relates to the labeling of PCR amplified viral nucleic acids(i.e. by using labeled PCR primers), in contrast to the cited reference's suggestion to use labeled probes; and (2) the claims invention relates to immobilized oligonucleotide probes, in contrast the cited reference suggesting use mobile probes which run across the sample. In addition, the claims recite specific oligonucleotide sequences with particular lengths which are not suggested in the cited references. The cited reference teaches probes and primers for detection of a codon 145 mutant and wildtype

(see page 28) which are different from the labeled primers and immobilized oligonucleotides recited in applicants' claimed invention. Accordingly, it would not have been obvious to one skilled in the art to make and/or use applicants' primers and oligonucleotides. Moreover, the claims recite oligonucleotides which are labeled with particular labels, such as Texas red or 6-FAM, which the cited reference neither teach, suggest or disclose. Accordingly, the cited reference does not render obvious applicants' claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 19-68.

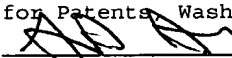
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone either of them at the number provided below.

No fee, other than the enclosed $1,696.00 fee which includes the $890.00 fee for a three-month extension of time and the $806.00 fee for additional claims, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Spencer H. Schneider
Registration No. 45,923
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



9-17-01

John P. White Date
Reg. No. 28,678
Spencer H. Schneider
Reg. No. 45,923

Exhibit A

Marked up version of paragraph on page 9, lines 14-35

--One of the applications of the present invention is the detection of the human hepatitis B virus surface antigen mutant 145 (Glycine to Arginine) using a solid glass supports device. In the present invention, further modifications have been added to two oligonucleotides (listed [in Claim 5] herein): 5'-TACGGACGGAAACT-3', and 5'-TACGGACAGAAACT-3', both located from position 582 to 595 as referred to the wild type human hepatitis B virus genome. These modifications include a fluorescent dye, 6-(fluorescein-6-carboxamido) hexanoate (6FAM), at its 5' terminus and a primary amine group at its 3' terminus. The resulting oligonucleotides that are immobilized on solid glass supports have the following structure: 5'-(6FAM)TACGGACGGAAACTGTTTTTTTTTTTT (C-7 amine)-3', and 5'-(6FAM)TACGGACAGAAACTGTTTTTTTTTTTT (C-7 amine)-3', and the second oligonucleotide contains the mutation G to A (position 8) leading to change at amino acid 145 (Glycine to Arginine) of human hepatitis B virus surface antigen. There is also an inclusion of a poly-T (underlined) as a synthetic linker aiming at facilitating the subsequent hybridization reaction with target human viral DNA sequences from serum samples.--

Markedup version paragraph on page 12, lines 21-30.

--For the novel detection system in the present invention,

polymerase chain reaction is carried out using either plasmid DNA (containing coding region of either wild type or mutant 145 (Glycine to Arginine) of human hepatitis B virus surface antigen), or viral DNA as indicated in Figure 1. Oligonucleotides used in the said polymerase chain reaction are listed [in Claim 1] herein and have the following localization on the wild type human hepatitis B viral genome:--

Markedup version of the paragraph page 14, line 31 to page 15, line 15.

--As a direct application of the novel detection system in the present invention, modifications have been added to two oligonucleotides (listed [in Claim 5] herein): 5'-TACGGACGGAAACT-3', and 5'-TACGGACAGAAACT-3', both located from position 582 to 595 as referred to the wild type human hepatitis B virus genome. These include a fluorescent dye, 6-(fluorescein-6-carboxamido) hexanoate, at its 5' terminus for microscopic detection and a primary amine group at its 3' terminus allowing its immobilization on solid glass supports. The resulting oligonucleotides that are immobilized on solid glass supports has the following structure: 5'-(6FAM)TACGGACGGAAACTGTTTTTTTTTTTT (C-7 amine)-3', and 5'-(6FAM)TACGGACAGAAACTGTTTTTTTTTTTT (C-7 amine)-3', and the second oligonucleotide contains the mutation G to A (position 8 of the oligonucleotide, in bold) leading to change at amino acid 145 (Glycine to Arginine) of human hepatitis B virus

surface antigen. There is also an inclusion of a poly-T (underlined) as a synthetic linker aiming at optimizing the subsequent hybridization reaction with target human viral DNA sequences from serum samples.--